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Claims 1-5 and 7-10 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,652,096 to Cimino, while Claim 11 stands rejected as allegedly being obvious in view of the combination of Cimino with U.S. Patent No. 5,082,934 to Saba *et al.* Applicants respectfully traverse the rejection, since neither Cimino nor Saba *et al.* disclose the nucleic acid probe employed in the presently-claimed method and, therefore, neither reference either alone or in combination support a conclusion of obviousness.

The photoactivatable cross-linking agent disclosed by Cimino is a thymidine monoadduct that comprises 8-methoxy psoralen attached to the nucleotide, thymidine. At column 7, lines 28-33, Cimino states:

The requisite furan side cis-syn 8-MOP:thymidine monoadduct was prepared and converted to its 5'-dimethoxytrityl-3'- β -cyanoethoxydiisopropylaminophosphoramidite derivative basically as described by Yabusaki *et al.*, U.S. Pat No. 4,599,303.

The oligonucleotides containing the monoadduct are disclosed at column 2, lines 18-20.

Thus, the nucleic acid probes taught by Cimino have a photoactivatable cross-linking agent that contains the sugar, deoxyribose; the base, thymine; and a psoralen group. This is in contrast to the nucleic acid probes of the presently-claimed invention in which the photoactivatable cross-linking agent does not include either a sugar or a base and occupies a nucleotide position between two nucleotides. As described in the specification at, e.g., page 9 lines 25-33, a sugar and base free compound (such as glycerol) and phosphoramidite chemistry is used to link the photoactive compound to the probe. A variety of photoactive compounds suitable for use in the invention are set

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forth at page 5, line 16 through page 6, line 11. The instant specification specifically exemplifies the use of a coumarin moiety as the photoactive compound, while later-filed U.S. Patent No. 6,303,799 describes the preparation of aryl olefin moieties which may also find use in the probes of the presently-claimed methods.

The nucleic acid probes taught by Saba *et al.* are also distinct from the probes employed in the instantly claimed methods. In the Abstract and at column 1, lines 1-10, Saba *et al.* disclose photoactivatable cross-linking agents that comprises a ribose or deoxyribose sugar and coumarin. Therefore, Saba *et al.* fails to teach or suggest a photoactivatable cross-linking agent that does not contain a sugar.

When rejecting claims under 35 U.S.C. § 103(a), the Examiner must establish a *prima facie* case of obviousness. See, e.g. *In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993); M.P.E.P. § 2142. The requirements for establishing a *prima facie* case of obviousness are: i) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; ii) there must be a reasonable expectation of success; and iii) the prior art reference (or references when combined) must teach or suggest all the claim limitations.

In the present case, the prior art, alone or in combination, does not disclose each of the claimed elements. Cimino discloses probes with cross-linking agents that contain sugars and bases, while Saba *et al.* discloses cross-linking agents that contain sugars. Therefore, the requirement of teaching or suggesting all the claim elements has not been met.

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Moving to the issue of whether the disclosures suggest that the elements be combined, Applicants respectfully submit that the elements are not disclosed, therefore, there can be no suggestion that they be combined to arrive at the present invention. Cimino makes no suggestion that the sugar or base can be eliminated. Similarly, Saba *et al.* discloses that various sugars can be utilized, at column 8, line 50, but makes no suggestion that the sugar can be eliminated.

Lastly, there is no reasonable expectation of success at arriving at the present invention by combining the two disclosures. At best, the compound of Saba *et al.* might be used in the methods of Cimino, although it is unclear from the cited references whether they would be sensitive enough to detect a single mismatch. As explained above, the photoactivatable cross-linking agents of the present claims are clearly distinguishable from Saba *et al.*, therefore, the skilled artisan would not be led to arrive at the present invention without undue experimentation from the disclosures of Cimino and Saba *et al.*

In view of these remarks, Applicants respectfully assert that the references relied upon by the Examiner do not establish a conclusion of obviousness and respectfully request that the rejection be withdrawn.

Claim 6 stands rejected under 35 U.S.C. § 103(a) as being obvious over Cimino in combination with European Patent No. EP 0 329 311 to Campbell. Specifically, the Examiner argues that Campbell teaches a method for detecting the presence of a mutation in a target nucleic acid wherein target nucleic acid is hybridized with a probe, and in particular that the target nucleic acid is generated by restriction digestion, and

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therefore, it would be obvious to one skilled in the art to have modified the method of Cimino to have generated the target nucleic acid by restriction enzyme digestion.

Applicants respectfully assert that Campbell does not disclose that a target nucleic acid is generated by restriction digestion. Rather, Campbell discloses a probe prepared by digestion with restriction enzymes (*see* page 10). Moreover, the arguments set forth above in response to the § 103(a) rejection of Claims 1-5 and 7-19 also apply in traversing the Examiner's rejection of Claim 6. Campbell may be relevant to the specific limitation as set forth in Claim 6 but it does not remedy the failure of Cimino and/or Saba *et al.* to teach or suggest the sugar- and base-free photoactivatable cross-linking agents employed in the presently-claimed methods.

Therefore, Applicants respectfully submit that the references, either alone or combination, do not support a conclusion of obviousness and respectfully request withdrawal of the rejection.

Lastly, Applicants submit herewith a Terminal Disclaimer, as suggested by the Examiner, thereby obviating Examiner's obviousness-type double patenting rejection based on related U.S. Patent No. 6,187,532.

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CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and an early notification of such is solicited. If, upon review, the Examiner feels there are additional outstanding issues, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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A handwritten signature in dark ink, appearing to read 'Todd A. Lorenz', is written over a horizontal line.

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